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Serial No.: 09/720,762 Confirmation No.: 5214
Applicant: Yanase, et al.
Title: GASKET WITH TAPERED SLANT FOR USE IN A PRE-FILLED SYRINGE
AND PRE-FILLED SYRINGE
Filed: December 28, 2000 Art Unit: 3746
Atty Docket: 114474.00014 Examiner: Hamo, Patrick

DECLARATION OF KEIZOU NAKAMOTO PURSUANT TO 37 C.F.R. § 1.132

I, Keizou Nakamoto, declare that:

1. I currently reside in Saitama, Japan, and make this declaration of my own knowledge and belief.
2. I am a Researcher Superintendent at EISAI, Co., Ltd, and have held this position for the past six years. Prior to my current position, I worked as a researcher for EISAI for 12 years. During my 18 years of employment with EISAI I have conducted research in the fields of injection agent technology and drug technology of solid drugs. Prior to my employment at EISAI, I received a master's degree in chemical engineering from Nagoya University in 1992.
3. I am a co-inventor of U.S. Patent Application No. 09/720,762 ("the '762 application") and am familiar with the subject matter of the application and what would have been known in the art at the time of the invention.
4. I have carefully read the February 12, 2010 Office Action issued by the Patent Office during prosecution of the '762 application and the references cited therein.
5. In order to address problems identified with previous gaskets, I and four other researchers at EISAI conducted a series of experiments between April 1997 and December

1997 to test syringe gaskets with different characteristics. Six different gasket shapes were developed and tested using Teflon-laminated gaskets made of different materials and JIS hardness.

6. The testing protocol was as follows: Each gasket was tested in a syringe barrel filled with either a contrast medium (IOM 300 mgI) or distilled water and sterilized at 115°C for 60 minutes. After drying, multiple tests were performed on each gasket and syringe, including a set of three tests that checked (1) gasket position; (2) the relative alignment of the gasket within the syringe ("crook"); and (3) the presence or absence of liquid leakage.

7. The gasket position was determined by measuring the distance from a collar surface of the syringe barrel to a gasket screw-side bottom surface using a gasket position inspector, a table-type gasket inspector, or a digital caliper. For 100 mg syringes, gaskets having gasket positions between 7.3 and 11.5 mm were considered acceptable, but gaskets positions measured at less than 7.3 mm were considered to have failed the test. For 50 mg syringes, gasket positions between 69.0 and 74.0 mm were considered acceptable, but positions measured at less than 69.0 mm were considered to have failed the test.

8. The crook of the gasket was determined by measuring the maximum value and the minimum value of the gasket position measurement for each gasket, the difference between these values being defined as the value of the crook. Gaskets having a crook value of 2 mm or less were considered acceptable and those with a value greater than 2 mm were considered to have failed the test.

9. With respect to testing the presence or absence of leakage, it was visually observed whether or not the contrast medium was leaking in a droplet form behind a contact part between the gasket and the syringe barrel. Those gaskets with no observed leakage were

considered acceptable and those with observable liquid leakage were considered to have failed the test.

10. The results of the testing described above are attached as Appendix 1 ("App. 1"). The first set of testing (Table 1) shows the test results of the six different shapes of gaskets ("A" to "F") having a JIS hardness of 48-51. The second set of testing (Table 2) used gaskets made of a different material with a similar hardness. The third set of testing (Table 3) used gaskets made of a third material but having a hardness of JIS 57-60. The fourth set of testing (Table 4) was limited to the two shapes of gaskets that showed the best results from the first three tests and having a JIS hardness of 57-59, but varying whether the liquid contact portion of the gasket was treated with silicone ("B2-41") or not ("B2-01").

11. From the four sets of testing, a final gasket type was selected: the "E" shape (which is shaped in accordance with the present invention) having a JIS hardness of 57-60. The fifth set of test results (Table 8) show the results of testing this selected gasket in both 100 mg and 50 mg syringes.

12. Below is a comparison of the testing results of the selected gasket shape made of D21-5-1 rubber, with one set of gaskets having a JIS hardness of 48-51 and the second set having a JIS hardness of 57-60. (See App. 1, Table 1 and Table 8.)

Comparison of Test Results

Gasket Shape: EP-15-E

Gasket Material: D21-5-1

Test No.	JIS Hardness	No. Gaskets Tested	Gasket Position Test		Crook Test		Leakage Test	
			Number Rejected	%	Number Rejected	%	Number Rejected	%
1	48-51	198	98	49.5	2	1.0	51	25.8
5	57-60	190 ¹	0	0	0	0	0	0

¹ Includes both 100 mg and 50 mg test results from Table 8.

13. As shown above, almost half (49.5%) of the gaskets with a JIS hardness of 48-51 were rejected for failing the position test, 1% failed the crook test, and 25.8% failed the leakage test. It was observed that many of the gaskets failed due to leakage or the changing of the gasket position within the syringe (leading to failure of the gasket position and/or the crook test) that occurred during the sterilization process.

14. In contrast, none of the gaskets in the final testing with a JIS hardness of 57-60 were rejected for failing the gasket position, crook or leakage tests. This is consistent with the other sets of testing performed, which also showed that an increase in JIS hardness to the range of 57-60 drastically reduced or eliminated testing failures due to gasket position, crook or leakage. Such a dramatic improvement was surprising and unexpected to me and my fellow researchers who performed the experiment.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Subject Application or any patent which issues thereon.

Signed on this 3 th day of August 2010.

Keizou Nakamoto
Keizou NAKAMOTO

APPENDIX 1

Table. 1 Effect of gasket type, material and hardness (EP-15-A~F, B2-00)

Gasket Material : D21-5-1 Hardness : 48-51

Filling fluid : 10W300mg/l Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	%	Gasket Position MIN	Crook (mm)			Dropjet	
	Gasket LOT NO		1) 2)			MIN	MAX	Average	Stdev	Number	%
37042201	EP-15-A	197	Abnormal position	49	24.8						
			Crooked gasket	18	8.1	9.14	0.31	3.59	1.75	0.31	-
			Total	65	32.9						
37042202	EP-15-B	198	Abnormal position	96	48.4						
			Crooked gasket	25	12.6	9.69	0.48	3.91	2.04	0.48	44
			Total	121	61.0						22.2
37042203	EP-15-C	198	Abnormal position	106	53.5						
			Crooked gasket	25	12.6	9.70	0.33	7.59	2.04	0.33	32
			Total	131	66.1						16.2
37042204	EP-15-D	198	Abnormal position	77	38.9						
			Crooked gasket	0	0.0	10.15	0.33	2.77	1.10	0.33	76
			Total	77	38.9						38.3
37042205	EP-15-E	198	Abnormal position	98	49.5						
			Crooked gasket	2	1.0	10.23	0.38	2.92	1.33	0.36	51
			Total	100	50.5						25.8
37042206	EP-15-F	198	Abnormal position	110	55.6						
			Crooked gasket	0	0.0	10.41	0.33	2.82	1.19	0.33	99
			Total	110	55.6						50.0

1) Abnormal position : less than 7.3 mm of total length between tale of barrel position and gasket's bottom position

2) Crookd gasket : OK $\leq 2\text{mm}$, NG $> 2\text{mm}$

Table.2 Effect of gasket type, material and hardness (EP-15-A~F, B2-41)

Gasket Material : D713GH Hardness : 48-52

Filling fluid : WFI Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	%	Gasket Position MIN	Crook (mm)				Drop test	
	Gasket LOT NO		1) 2)				MIN	MAX	Average	Stdev	Number	%
37072301	EP-15-A 970356	19	Abnormal position	4	21.1							
			Crooked gasket	14	73.7	6.63	0.50	2.19	1.64	0.42	No Detect	
			Total	14	73.7							
37072302	EP-15-B 970357	20	Abnormal position	1	5.0							
			Crooked gasket	4	20.0	7.05	0.01	2.31	0.96	0.56	No Detect	
			Total	4	20.0							
37072303	EP-15-C 970358	20	Abnormal position	2	10.0							
			Crooked gasket	3	15.0	7.05	0.33	2.66	1.25	0.62	No Detect	
			Total	3	15.0							
37072304	EP-15-D 970359	20	Abnormal position	0	0.0							
			Crooked gasket	0	0.0	7.86	0.19	1.29	0.81	0.34	3	15.0
			Total	0	0.0							
37072305	EP-15-E 970360	20	Abnormal position	0	0.0							
			Crooked gasket	0	0.0	8.07	0.13	1.22	0.69	0.30	0	0.0
			Total	0	0.0							
37072306	EP-15-F 970361	20	Abnormal position	0	0.0							
			Crooked gasket	0	0.0	8.24	0.05	1.03	0.45	0.24	0	0.0
			Total	0	0.0							

1) Abnormal position : less than 7.3 mm of total length between tale of barrel position and gasket's bottom position

2) Crookd gasket : OK $\leq 2\text{mm}$, NG $> 2\text{mm}$

Table.3 Effect of gasket type, material and hardness (EP-15-A~F, B2-41)

Gasket Material : D21-6-1 Hardness (57-60)

Filling fluid : HF1 Volume : 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	%	Gasket Position MIN	Crook (mm)				Droplet	
	Gasket LOT NO		1) 2)				MIN	MAX	Average	Stddev	Number	%
			Abnormal position	0	0.0							
37072401	EP-15-A	20	Crooked gasket	0	0.0	7.83	0.03	0.63	0.26	0.18	No Detect	
	970350		Total	0	0.0							
			Abnormal position	0	0.0							
37072402	EP-15-B	20	Crooked gasket	0	0.0	7.97	0.03	0.57	0.24	0.16	No Detect	
	970351		Total	0	0.0							
			Abnormal position	0	0.0							
37072403	EP-15-C	20	Crooked gasket	0	0.0	9.11	0.03	0.95	0.25	0.27	No Detect	
	970352		Total	0	0.0							
			Abnormal position	0	0.0							
37072404	EP-15-D	20	Crooked gasket	0	0.0	9.65	0.03	0.49	0.16	0.12	1	5.0
	970353		Total	0	0.0							
			Abnormal position	0	0.0							
37072405	EP-15-E	20	Crooked gasket	0	0.0	9.57	0.03	0.44	0.19	0.11	0	0.0
	970354		Total	0	0.0							
			Abnormal position	0	0.0							
37072406	EP-15-F	20	Crooked gasket	0	0.0	9.78	0.01	0.65	0.17	0.15	0	0.0
	970354		Total	0	0.0							

1) Abnormal position : less than 7.3 mm of total length between tale of barrel position and gasket's bottom position
 2) Crooked gasket : OK $\leq 2\text{mm}$, NG $> 2\text{mm}$

Table 4 Effect of gasket type, material and hardness (EP-15-E, F B2-01-B2-41)
Gasket Material ; D21-5-1 Hardness UP Hardness ; (57-59)
Filling fluid ; WFI and (ION300mg/l) Volume ; 102ml

LOT NO	Type of gasket	Number of Sample	Reason of Rejection	Number	%	Gasket Position MIN	Crook (mm)				Droplet	
	Gasket LOT NO		1) 2)				MIN	MAX	Average	Stdev	Number	%
	EP-15-E		Abnormal position	0	0.0							
37091709	970551	40	Crooked gasket	0	0.0	8.01	0.33	1.03	0.61	0.16	0	0.0
(WFI)	B2-41		Total	0	0.0							
	EP-15-E		Abnormal position	0	0.0							
37101301	970646	99	Crooked gasket	0	0.0	7.79	0.04	0.82	0.38	0.16	0	0.0
(ION300)	B2-01		Total	0	0.0							
	EP-15-E		Abnormal position	0	0.0							
37101302	970640	99	Crooked gasket	0	0.0	8.26	0.10	1.14	0.41	0.22	1	1.0
(ION300)	B2-41		Total	0	0.0							
	EP-15-F		Abnormal position	0	0.0							
37091710	970552	40	Crooked gasket	0	0.0	7.73	0.31	1.07	0.60	0.20	0	0.0
(WFI)	B2-41		Total	0	0.0							
	EP-15-F		Abnormal position	0	0.0							
37101303	970647	100	Crooked gasket	0	0.0	7.89	0.11	1.04	0.46	0.23	14	14.0
(ION300)	B2-01		Total	0	0.0							
	EP-15-F		Abnormal position	0	0.0							
37101304	970641	100	Crooked gasket	0	0.0	8.34	0.12	0.89	0.44	0.19	6	6.0
(ION300)	B2-41		Total	0	0.0							

1) Abnormal position : less than 7.3 mm of total length between tale of barrel position and gasket's bottom position
2) Crooked gasket : OK $\leq 2\text{mm}$, NG $> 2\text{mm}$

Table.8 Evaluation of gasket position, crook and droplet in 10W300S-100, 50
Gasket Material : D21-5-1 Hardness : 57-60

LOT NO	Type of Gasket Gasket LOT NO	Number of Samples	Reason of Rejection 1) 2) 3)	Number	%	Gasket Position RTN		Crook (mm)				Droplet	
						MIN	MAX	Average	Stdev	Number	%		
10W300-100	EP-15-E		Abnormal position	0	0.0								
	37110701	B2-01	100	Crooked gasket	0	0.0	7.05	0.07	1.26	0.40	0.21	0	0.0
	970688		Total	0	0.0								
10W300-50	EP-15-E		Abnormal position	0	0.0								
	37121501	B2-01	80	Crooked gasket	0	0.0	71.05	0.04	0.98	0.25	0.18	0	0.0
	970772		Total	0	0.0								

- 1) 100mm Abnormal position : less than 7.3 mm of total length between tale of barrel position and gasket's bottom position
 2) 50mm Abnormal position : less than 69.00 mm of total length between tale of barrel position and gasket's bottom position
 3) Crooked gasket : OK $\leq 2\text{mm}$, NG $> 2\text{mm}$